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Transfusion strategy in multiple trauma patients

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Abstract: **PURPOSE OF REVIEW** To point out the tolerance of anemia, the possible use of alternatives to allogeneic blood products as well as the pathophysiological effects of transfusions in the context of multiple trauma patients. **RECENT FINDINGS** Restrictive transfusion triggers are beneficial for patient outcome in trauma. The actual European Trauma Treatment Guidelines suggest the use of point-of-care devices, the use of transfusion algorithms and factor concentrates to control coagulopathy. The use of high ratios of plasma to red blood cells to improve survival has been shown to suffer from a time-dependent survival bias. In massive bleeding, factor-based treatment of coagulopathy is feasible and preferable to plasma transfusion, if available. In nonmassive bleeding, allogeneic transfusion of blood products increases the appearance of serious adverse events and mortality and should be avoided unless clearly indicated. **SUMMARY** Transfusion in trauma has to be an individual decision for a specific patient, not for a specific laboratory value. Transfusion management must aim at reducing or even avoiding the use of allogeneic blood products. This may lead to a new gold standard with cost reduction and amelioration of outcome of major trauma patients.

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Transfusion strategy in multiple trauma patients

Oliver M. Theusinger, Philipp Stein, and Donat R. Spahn

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To point out the tolerance of anemia, the possible use of alternatives to allogeneic blood products as well as the pathophysiological effects of transfusions in the context of multiple trauma patients.

Recent findings

Restrictive transfusion triggers are beneficial for patient outcome in trauma.

The actual European Trauma Treatment Guidelines suggest the use of point-of-care devices, the use of transfusion algorithms and factor concentrates to control coagulopathy. The use of high ratios of plasma to red blood cells to improve survival has been shown to suffer from a time-dependent survival bias. In massive bleeding, factor-based treatment of coagulopathy is feasible and preferable to plasma transfusion, if available. In nonmassive bleeding, allogeneic transfusion of blood products increases the appearance of serious adverse events and mortality and should be avoided unless clearly indicated.

Summary

Transfusion in trauma has to be an individual decision for a specific patient, not for a specific laboratory value. Transfusion management must aim at reducing or even avoiding the use of allogeneic blood products. This may lead to a new gold standard with cost reduction and amelioration of outcome of major trauma patients.

Keywords

allogeneic blood products, assessment of anemia, pathophysiology of transfusions, transfusion triggers, trauma

INTRODUCTION

Mortality related to trauma may be up to 40% in the civilian sector [1[•],2,3]. Of those 40%, one quarter of the deaths are related to coagulopathy and uncontrolled blood loss that may be preventable [4[•],5]. For this reason, treatment of coagulopathy and hemostatic control are key to reduce mortality due to exsanguination, to save blood products and to improve outcome [1[•],6–11].

Using restrictive transfusion triggers and patient-specific physiological reserve of anemia are the two aspects that can also be applied in multiple trauma patients to reduce the use of blood products [12[•],13[•],14[•],15,16[•]].

Point-of-care (POC) devices, such as rotational thromboelastometry (ROTEM, TEM Innovations GmbH, Munich, Germany) or thromboelastography (TEG, Haemoscope Corporation, Niles, Illinois, USA) are becoming more popular to treat bleeding in trauma and are highly recommended to guide hemostatic therapy during coagulopathy [1[•],17,18].

The purpose of this review is to enlighten patient tolerance to anemia, the use of transfusion algorithms and alternatives to allogeneic blood products, the outcome of transfused patients,

complications and pathophysiological effects of blood products as well as transfusion triggers and thresholds to use blood products in a restrictive manner.

PATHOPHYSIOLOGICAL EFFECTS OF TRANSFUSION

Although blood transfusions are considered to be well tolerated in first world countries with regard to the direct transmission of infectious agents, there are still some serious adverse events that need to be mentioned. Although their frequency is low, hemolytic and delayed hemolytic reactions are severe adverse events [19]. They may be due to the transfusion of ABO incompatible blood product. Delayed

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KEY POINTS

- Also, in trauma, restrictive transfusion triggers are beneficial for patient outcome.
- Goal-directed transfusion algorithms and the use of POC devices in trauma reduce the need of allogeneic blood products.
- There is no clear evidence for high FFP : RBC ratios as this concept suffers from a time-dependent survival bias in patients receiving high FFP : RBC ratios.

hemolytic reactions occur in patients who have developed antibodies from previous (ABO compatible) transfusions or pregnancy. These antibodies in question sometimes present in low concentrations and are too weak to be detected by standard procedures at the time of antibody screening before the intended transfusion. Subsequent transfusion with red blood cells (RBCs) having the corresponding antigen results in an anamnestic antibody response and consecutive hemolysis of transfused RBCs. Febrile reactions (a rise of 1.0 °C from baseline) due to cytokines and antibodies to leukocyte antigens reacting with leukocytes or leukocyte fragments are common with a frequency of about 10% [19]. Foreign plasma proteins are able to cause allergic reactions causing urticaria and may be associated with laryngeal edema and bronchospasm; their frequency is about 1%. Anaphylactic reactions are rare and may be due to an anti-immunoglobulin A reaction, leading to cardiovascular instability, dyspnea, stridor, shock and possible cardiac arrest. Transfusion-related acute lung injury (TRALI) is underrecognized, and thus its frequency is rare [20[¶]]. The pathomechanism is supposed to be linked to the presence of antibodies in the donor plasma, which react with the recipient's leukocyte antigens or induce the production of inflammatory mediators resulting in a noncardiogenic pulmonary edema with a 10% fatality [21,22[¶]]. Bacterial contamination occurs when a small number of bacteria enter a blood component during collection or processing. During storage, bacteria may proliferate, resulting in a large number of organisms and endotoxins being given with the transfusion. This complication is rare in first world countries but leads to major complications including fatalities [23[¶]].

In addition to the above-mentioned distinctive side-effects, RBC transfusions in trauma patients increase the risk of multiorgan failure, infections, renal dysfunction, length of stay (LOS) and mortality [24,25] .

Trauma patients are at greater risk for massive transfusion. In addition, longer storage time of RBCs

[26–28] leads to even longer LOS [29,30], additional occurrence of deep vein thrombosis [31] and even higher mortality [26,30–33] with a possible dose effect regarding older blood products [27,31,33].

ASSESSMENT OF ANEMIA IN TRAUMA

The initial hemoglobin or hematocrit measurement is not a precise measure of the actual blood loss of a trauma victim, particularly after a limited initial fluid therapy. Therefore, a near normal hematocrit value in the emergency department does not rule out significant blood loss (low sensitivity) [34]. But, a primarily low hematocrit has a high specificity in identifying major injury and blood loss requiring operative intervention [34,35]. Moreover, a low hematocrit is associated with higher injury severity scores, hypotension and acidosis [36]. Preexisting anemia or severe hemodilution cannot be ruled out as other reasons for a low hematocrit, but a drop in the hematocrit value over time (serial measurement) is sensitive and specific for bleeding, even in the context of fluid resuscitation [37].

In 2002, Kinoshita *et al.* [38] were the first to describe an apparatus to measure hemoglobin concentrations noninvasively using three different wavelengths. The development of multiwavelength pulse oximeters showed promising results and a relatively acceptable accuracy in perioperative patients when peripheral perfusion, indexed as signal quality by the machine, was good (in 70% of cases) [39]. However, for trauma patients, this method is inadequate as shock, hypothermia and vasoconstriction influence the results [40,41[¶]]. In a study comprising 525 trauma patients, detection of a hemoglobin value was impossible only in 34% of the readouts [42].

Although noninvasive hemoglobin measurement shows promising results in patients with an adequate peripheral perfusion, it is not yet useful in the setting of trauma and hemorrhagic shock to guide transfusion decision making.

TRANSFUSION TRIGGERS AND THRESHOLDS (THE EMPIRICAL APPROACH)

Blood transfusion historically is thought to save the life of bleeding patients, but no high evidence data are available to date to support this axiom [43].

In the perioperative setting, not referring specifically to trauma victims, anemic patients have a significantly higher perioperative 30-day mortality after major noncardiac surgery, compared to controls with normal hemoglobin levels [44,45].

However, allogeneic blood transfusion is not the 'cure' for the anemic patient. Specific risks, such as (viral) infection, TRALI, transfusion-related circulatory overload and immunomodulation, account for the transfusion-associated worsened outcome [46,47].

Formerly accepted hemoglobin transfusion triggers of about 100 g/l were abandoned [48].

A Cochrane review concerning transfusion triggers states that blood transfusion probably can be withheld to hemoglobin levels of as low as 70 g/l. The threshold for patients with coronary artery disease remains to be exactly determined but is likely at or below 80 g/l. Further research is needed to evaluate the role of even lower hemoglobin levels [9]. A randomized controlled multicenter study showed a lower mortality, fewer complications and a shorter length of hospital stay in patients with acute upper gastrointestinal bleeding when transfused restrictively (Hb <70 g/l) as compared with a more liberal transfusion regimen (Hb <90 g/l) [49[■]]. In hip fracture surgery patients with a history of, or risk factors for, cardiovascular disease, liberal transfusion strategy (threshold 100 g/l) did not reduce rates of death on 60-day follow-up or reduce in-hospital morbidity in elderly patients [50].

In 203 trauma patients, analyzed as a subgroup of the prospective randomized controlled 'transfusion requirements in critical care' trial [51], a restrictive transfusion trigger (<70 g/l) to maintain hemoglobin between 70 and 90 g/l was not inferior to a liberal (>100 g/l) regimen with hemoglobin concentrations between 100 and 120 g/l. Patients in the restrictive group received significantly fewer allogeneic RBC transfusions. Reported 30-day all-cause mortality, rate of multiorgan dysfunction, LOS in the hospital and in the ICU were comparable and not significantly different between the two groups [51].

In patients with traumatic brain injury (TBI), RBC transfusion increased local brain tissue oxygen partial pressure in 74% of the patients [52]. However, this effect was not seen with 'old' blood stored more than 19 days [53]. Despite increased oxygen partial pressure, no positive effect on cerebral metabolism was seen [54]. More days with a hematocrit below 30% were associated with improved neurologic outcomes in a retrospective analysis of 169 patients [55]. Transfusion, but not anemia, significantly led to higher mortality and more complications among 1150 TBI patients [56]. Increasing the hematocrit above 28% in the initial operation phase following severe TBI was not associated with an increased or decreased morbidity or mortality [57]. Initial anemia (Hb <100 g/l) in the emergency

department following TBI was not a mortality risk factor [58].

The current knowledge gives no compelling evidence to treat patients with severe TBI differently in contrast to other critically ill patients concerning RBC transfusion [1[■]].

Clinical indicators such as injury severity score above 25, the need for procedural bleeding control [59[■]] and multiple scoring systems consisting of international normalized ratio (INR), mechanism of injury, positive results for focused assessment with sonography for trauma, blood pressure, initial hemoglobin and heart rate can help identify trauma patients at risk for massive transfusion, but also patients highly unlikely to need a massive transfusion [60[■],61]. These variables and scores may be used as an adjunct to guide resuscitation, but they do not reflect the specific needs of an individual trauma victim.

Emphasis must be put on the fact that transfusion has to be an individual decision for a specific patient at a specific moment in time, not for a specific hemoglobin value, and RBC transfusion must be avoided whenever possible.

ACUTE ANEMIA, HEMODILUTION AND ANEMIA TOLERANCE (THE INDIVIDUAL PHYSIOLOGICAL APPROACH)

Only 0.3 ml of oxygen is dissolved physically in 100 ml of blood at room air breathing (FiO₂ 0.21 and atmospheric pressure 1013 mbar), but it can play a vital role in severe acute anemia states. With a FiO₂ of 1.0 and a hemoglobin value of 10 g/l, the physically dissolved amount of oxygen equals the amount of oxygen bound to hemoglobin [62]. Survival of transient acute anemia (hemoglobin 7 g/l) was reported [63]. Even without allogeneic blood transfusion, a nadir hemoglobin of 14 g/l was survived by a patient refusing blood products [64].

Cellular and circulatory physiological compensatory mechanisms facilitate vital oxygen delivery to the tissues (DO₂) during anemia [65[■]]. DO₂ is the product of cardiac output and arterial oxygen content of the blood. The body's demand for oxygen is five-fold exceeded by DO₂ in physiological conditions. Moreover, a rise in cardiac output and an increase in O₂ extraction can compensate for a decline in the oxygen content of the blood in states of acute anemia [66].

A critical hemoglobin value [Hb(crit)] is reached when whole body oxygen consumption (VO₂) starts to decline because of insufficient DO₂ (=global body hypoxia). In an animal model, all of the study pigs consecutively died within 3 h after reaching the

Hb(crit) with a FiO₂ of 0.21 [67]. Increasing the FiO₂ leads to more physically dissolved oxygen, resulting in a lower Hb(crit) and a higher level of possible hemodilution [68[°]].

In addition, Lauscher *et al.* [69[°]] demonstrated that there are organ-specific thresholds of anemic hypoxia in anesthetized pigs. Kidney and skeletal muscle showed tissue hypoxia before reaching Hb(crit) and significantly earlier than cardiac ventricle and brain. On the contrary, the liver showed even fewer cellular signs of hypoxia at a hemoglobin level of 40 g/l compared with the control group (normal hemoglobin values) [69[°]]. The impact of this animal model data is unclear for the time being. Further investigations need to be performed to elucidate the clinical relevance in the human body. Moreover, current transfusion thresholds (70 g/l) are high above the critical individual organ margin described in the animal study.

Other clinically susceptible factors to increase anemia tolerance are deep neuromuscular blockade [70], hypothermia, by reducing (cerebral) oxygen consumption by 6% per degree Celsius [71] and administration of norepinephrine to overcome arterial hypotension during hemodilution [72].

This growing knowledge may lead to a better understanding of the role of transfusion in the context of severe traumatic bleeding. Measures to increase anemia tolerance, further insights into organ-specific oxygen demand and assessment of organ ischemia thresholds may reveal new physiologic triggers to guide red cell transfusion therapy in the future.

ALTERNATIVES TO ALLOGENEIC BLOOD PRODUCTS

Actual studies clearly show that a high amount of RBCs, fresh frozen plasmas (FFPs) and platelets can be reduced without additional risks for patients by using transfusion algorithms in trauma on the basis of coagulation factor concentrates [73,74]. Data from four European countries (United Kingdom, Germany, Italy and Switzerland) were used to calculate blood substitution and costs of blood products needed. The results showed that these products account for approximately one third of all costs associated with trauma care [75]. The reduction of septic complications and organ failure tends to reduce days on ventilator, whilst on ICU and shorten overall in-hospital LOS which clearly contribute to cost reduction in trauma care without increasing the risk of patients [76].

The use of POC devices as well as goal-directed algorithms is getting essential (Fig. 1)

[77[°]]. Because of their use, coagulopathy in trauma can be treated early and effectively and blood loss and the use of blood products can be reduced [1[°],78[°],79[°]].

Thromboelastometry (ROTEM) measures and graphically displays the viscoelasticity of the developing blood clot. The first usable results are provided within 5–10 min, whereas the classical laboratory results may take from 30 to 90 min and thereby delay effective therapy for patients [77[°]]. Details on the ROTEM method and technology are to be found in the literature [80]. Another device to be used is the thromboelastography (TEG, Haemoscope Corporation, Niles, Illinois, USA) working similarly to the ROTEM, details are described in the literature [81]. The use of POC devices is acutely clearly recommended by the European Trauma Guidelines [1[°]].

The use of FFP leads to adverse effects that are similar to those of RBCs (increased mortality, multiple organ failure, infections, lung injury, immunomodulation) [82[°]]. The use of FFP is getting more and more questionable as concentrations of factors are variable and large volumes are necessary to achieve an effect. Actually, the use of fibrinogen concentrates is favorable compared with FFPs [83]. According to the European Trauma Guidelines, the use of FFP or fibrinogen is indicated in patients with massive transfusions. A ratio of 1:2 (FFP:RBC) is suggested if FFP is being used. However, in non-massive bleeding, plasma transfusion should be avoided [1[°]]. Fibrinogen has been shown to be the coagulation factor which drops critically first during bleeding; for this reason, its concentration needs to be monitored closely [1[°],73,84]. The actual recommended fibrinogen target levels of 1.5–2.0 g/l have been defined by the European Trauma Treatment Guidelines [1[°]]. As the concentration of fibrinogen in FFP does not exceed 2 g/l, the use of fibrinogen concentrates has the advantage of reaching fibrinogen levels above 2.0 g/l without volume overload [85]. The second coagulation factor to be monitored closely is factor XIII which, in combination with fibrinogen, is essential for a stable clot; its level should be maintained above 60% by administration of factor concentrate in case of active bleeding [86–89]. In addition to those single-factor concentrates, prothrombin complex concentrates may be taken into consideration [73,89–93]. There are different types of prothrombin complex concentrates regarding factors contained (three vs. four), their relative composition and their thrombotic potential. Their use in trauma is recommended since 2013, but only under strict surveillance by rotational thromboelastometry and in the context of algorithms, which suggest small and repeated


Diagnostic	Intervention
Preoperative history <ol style="list-style-type: none"> Drugs affecting coagulation <ul style="list-style-type: none"> Antiplatelet drugs Heparin Oral anticoagulation (Vit. K antagonists, Xa antagonists, IIa antagonists) Coagulation status? HIT II? 	ROTEM after anesthesia induction <ul style="list-style-type: none"> Transplant surgery Cardiac and vascular surgery Difficult cancer surgery Liver insufficiency Intra-abdominal sepsis Emergency room entry
Blood loss > 50% with diffuse bleeding	
ROTEM analysis <ul style="list-style-type: none"> EXTEM, INTEM, FIBTEM, APTM HEPTEM in heart and vascular surgery 	Target values <ul style="list-style-type: none"> Normothermia (temp. > 35°C) Normocalcemia (Ca > 1.15 mmol/l) No acidosis (pH > 7.2) Hematocrit > 0.21 Hypotension (MAP 55–60 mmHg) Crystalloid and/or colloid volume substitution
FIBTEM < 7 mm	Fibrinogen 2–4 g i.v. (maximal 3x2g), after a total of 6 g give FXIII
INTEM (CT and CFT prolonged) and HEPTEM normal OR ACT pathological and heparinase ACT normal	Protamine sulfate 1:1 to heparin crystalloid and colloid volume substitution
EXTEM / INTEM Decrease of MCF after maximum was reached APTEM: normal  Hyperfibrinolysis	Tranexamic acid <ul style="list-style-type: none"> 15 mg/kg BW as bolus i.v. 1–2 mg/kg/h during surgery i.v. as perfusion
On-going diffuse bleeding	
EXTEM /INTEM MCF<40 mm CT EXTEM /INTEM normal MCF FIBTEM <7 mm Hct > 0.21 MCF FIBTEM > 7mm Platelets < 50 000/ µl (< 100 000/ µl in cardiac surgery or in patients suffering from traumatic brain injury)	Fibrinogen up to 6 g, followed by Factor XIII 15 U/kg BW crystalloid and colloid volume substitution Platelet concentrates Target of Factor XIII: > 60% (Factor XIII 15 U/kg BW) Target of Factor V: >20% (in particular in liver insufficiency /trauma or intra-abdominal sepsis: 2–4 U FFP)
On-going diffuse bleeding	
Quick's value < 30% and Factor V > 20 % OR EXTEM/INTEM: CT, CFT prolonged	4 factor prothrombin complex concentrate 1000–2000 IU <ul style="list-style-type: none"> Factor II, VII, IX and X Depending on the patient's bodyweight
In case of massive transfusion	Target hematocrit: 0.21–0.24
If massive diffuse bleeding continues and	
Treated acidosis Treated hypothermia Excluded hypocalcemia Hematocrit: 0.21–0.24 Excluded DIC Fibrinogen was substituted Platelets >50 000/ l (>100 000/ l in cardiac surgery or in patients suffering from traumatic brain injury)	Recombinant Factor VIIa 60 µg/kg bodyweight i.v. A second dose of 60 µg/kg bodyweight i.v. can be given again after 2–4 hours, if bleeding has not completely stopped.

FIGURE 1. Third version of the transfusion algorithm of the University Hospital of Zürich 2013, Switzerland. BW, body weight; CFT, clot formation time; FFP, fresh frozen plasma; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; i.v., intravenous; MAP, mean arterial pressure; MCF, maximal clot firmness. Adapted with permission [77[■]].

doses to prevent thromboembolic adverse events [1st,92].

In addition to all factor concentrates, one should take the two following drugs into consideration: first, tranexamic acid (TXA), which stops hyperfibrinolysis, reduces the need for blood products and decreases mortality [94] and second, desmopressin, which enhances platelet adherence [94–99]. There is actually clear evidence that the early use of TXA is favorable for patients. One study, including 40 trauma patients (55% penetrating, 45% blunt trauma), all received TXA in the prehospital setting showing that this is feasible without delaying treatment or creating severe adverse events [100th]. However, patients' outcome could not be assessed because of the study design and the limited sample size. The most known study, named CRASH-2, showed that early (within first 3 h) administration of TXA in the emergency room reduces mortality significantly [94]. Furthermore, TXA is cost effective and has been integrated into military trauma algorithms [101th]. A recent systematic Cochrane review showed that TXA clearly reduces blood transfusions in patients requiring emergency or urgent surgery [102th].

Regarding desmopressin, the European Trauma Guidelines recommend a single dose for trauma patients treated with aspirin [1st].

TRANSFUSION AND PATIENT OUTCOME

Today, in many countries, the widespread approach is to transfuse bleeding trauma patients with FFP and RBCs at a 1 : 1 ratio. Halmin *et al.* [103] recently published a cohort study on the association between death in trauma and FFP:RBC ratio integrating time-dependent data, as suggested by Ho *et al.* [104]. In their retrospective cohort study including nearly 750 patients from one single trauma center, they analyzed time-dependent transfusions and the relative risk of death comparing low and high FFP:RBC ratios. They could find no significant association between the low plasma ratio and the risk of death. On the other side, when analyses were made excluding the time factor, a strong effect of high plasma ratios was seen, clearly pointing out a survival bias [103]. This high FFP:RBC regimen is supported by observational studies mainly from recent wars, showing lower mortality in bleeding patients receiving equal volumes of plasma and RBCs as compared with patients treated with a lower FFP:RBC ratio. The rationale for this practice is still unclear with several studies failing to show any survival benefits of increased plasma use, perhaps because of a failure to account for the timing of transfused units. The FFP:RBC ratio measured 24 h

after admission was based primarily on war casualties, in which it was realized that RBCs alone have no effect on coagulation but the addition of FFP ameliorates coagulation.

The observation of a higher survival rate in patients having received an equivalent number of FFP and RBC transfusion at 24 h after admission, however, suffers from this 'survival bias'. Several studies have addressed this issue. Ho *et al.* [104,105] were able to show that there is a time-dependent covariate regarding high FFP:RBC ratios and so far, the current available evidence is inconclusive. Any retrospective analysis favors patients having received high FFP:RBC ratio because only they survived long enough to receive high amounts of FFP. Those dying early did not survive long enough to have FFPs being ready to be administered [106,107th]. This dilemma can only be solved with prospective randomized studies. Nascimento *et al.* [107th] indeed published in 2013 such a prospective randomized controlled study with 78 patients assessing the feasibility of such a study and the effect on mortality and complications in severe trauma patients. Patients were randomly assigned to a fixed ratio of 1 : 1 : 1 transfusion (1 unit of RBC, FFP and platelets) ($n = 40$) or to a laboratory guided transfusion protocol which served as the control group ($n = 38$) [107th]. The all-cause 28-day mortality was 32% in the fixed-ratio group compared to 14% in the control group and thus increased by a relative risk of 2.27 (95% CI 0.98–9.63). Event-free survival was 54% in the patients with fixed ratios compared to 78% in the control group ($P = 0.053$). The fixed-ratio transfusion protocol was feasible but associated with large plasma wastage and a near significantly higher mortality [107th].

There is a great need for further studies on this subject to clearly identify the optimal treatment of massively bleeding trauma patients. Furthermore, it has recently been shown that there is a clear causation between blood transfusions and bad outcome, this may also be true in trauma patients and thus one should consider giving as little blood as possible and as much as necessary in order to have a better outcome [108]. This can be guided by a clear algorithm that has to be followed by the whole staff in charge. Theusinger *et al.* [77th] recently published a good example for a feasible algorithm.

CONCLUSION

Transfusion in trauma has to be an individual decision for a specific patient, not for a specific laboratory value. Transfusion management must aim on reducing or even avoiding the use of allogeneic blood products. This may lead to a new gold

standard with cost reduction and amelioration of outcome of major trauma patients.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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This study is the updated version of the European Trauma guideline published in 2007 and updated in 2010. Key changes include new recommendations on the appropriate use of vasopressors and inotropic agents and reflect an awareness of the growing number of patients in the population at large treated with antiplatelet agents and/or oral anticoagulants. A significant addition is a new section that discusses the need for every institution to develop, implement and adhere to an evidence-based clinical protocol to manage traumatically injured patients. The remaining recommendations have been reevaluated and graded based on literature published since the last edition of the guideline. Consideration was also given to changes in clinical practice that have taken place during this time period as a result of both new evidence and changes in the general availability of relevant agents and technologies.

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This study deals with the fact that traumatic injuries worldwide are responsible for over 5 million deaths annually. Bleeding caused by traumatic injury-associated coagulopathy is the leading cause of potentially preventable death among trauma patients. Despite these facts, awareness of this problem is insufficient and treatment options are often unclear. The STOP the Bleeding Campaign, therefore, aims to increase awareness of this fact and its appropriate management by publishing European guidelines for the management of the bleeding trauma patient, by promoting and monitoring the implementation of these guidelines and by preparing promotional and educational material, organizing activities and developing health quality management tools. The campaign aims to reduce the number of patients who die within 24 h after arrival in the hospital due to exsanguination by a minimum of 20% within the next 5 years.

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